Exhibit 5

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Prospects

Cytokines and hematopoietic stem cell mobilization

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KEYWORDS

stem cell • mobilization • transplantation

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) has become the standard of care for the treatment of many hematologic malignancies, chemotherapy sensitive relapsed acute leukemias or lymphomas, multiple myeloma; and for some non-malignant diseases such as aplastic anemia and immunodeficient states. The hematopoietic stem cell (HSC) resides in the bone marrow (BM). A number of chemokines and cytokines have been shown in vivo and in clinical trials to enhance trafficking of HSC into the peripheral blood. This process, termed stem cell mobilization, results in the collection of HSC via apheresis for both autologous and allogeneic transplantation. Enhanced understanding of HSC biology, processes involved in HSC microenvironmental interactions and the critical ligands, receptors and cellular proteases involved in HSC homing and mobilization, with an emphasis on G-CSF induced HSC mobilization, form the basis of this review. We will describe the key features and dynamic processes involved in HSC mobilization and focus on the key ligand-receptor pairs including CXCR4/SDF1, VLA4/VCAM1, CD62L/PSGL, CD44/HA, and Kit/KL. In addition we will describe food and drug administration (FDA) approved and agents currently in clinical development for enhancing HSC mobilization and transplantation outcomes. J. Cell. Biochem. © 2006 Wiley-Liss, Inc.

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ARTICLE TEXT

The development of hematopoietic stem cell transplantation (HSCT) has been crucial to support the administration of high doses of chemotherapy and radiation therapy for patients undergoing autologous (auto-SCT) or allogeneic stem cell transplant (allo-SCT). An extra benefit of allo-SCT is that it may enhance immune reconstitution while generating a graft-versus tumor effect to clear residual tumor cells. The most common indications for auto-SCT are relapsed chemotherapy sensitive non-Hodgkin's lymphoma or multiple myeloma. Allo-SCT is the preferred strategy for the treatment of high-risk acute leukemias in remission, or chemotherapy sensitive relapsed acute leukemias. The HSC resides in the BM, however, in the last years we have learned how to enhance trafficking of hematopoietic stem cell (HSC) into the peripheral blood in simple and safe ways. The recruitment of HSCs from the BM into peripheral blood is termed HSC mobilization [Cashen et al., [2004]]. These HSC are capable of homing to the BM cavity and regenerating a full array of hematopoietic cell lineages in a timely fashion after ablative and non-myeloablative conditioning. This process mimics enhancement of the

physiological release of HSC from the BM reservoir in response to stress signals during injury and inflammation.

It was recognized in the 1960s that a small number of HSCs circulated in the peripheral blood during steady-state homeostasis [Goodman and Hodgson, [1962]]. In the 1970s an increase in circulating HSC was observed after chemotherapy treatment. In the early 1980s the first autologous stem cell transplants using mobilized Peripheral blood stem cell (PBSC) collected by apheresis were documented [Kessinger et al., [1986]]. Initially, the mobilization protocols used chemotherapy alone; however, since the discovery and clinical development of human G-CSF [Welte et al., [1985]] cytokine mobilization has become the standard of care. Currently, the unique cytokines approved by the food and drug administration (FDA) for autologous and allogeneic stem cell mobilization are granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). PBSC mobilization and collection have been optimized in different clinical trials, nevertheless, 14% of patients receiving standard mobilization for the purpose of autologous donation and 4% for allogeneic donors still fail to mobilize [Moncada et al., [2003]].

In this article we will discuss the mechanisms involved in stem cell mobilization, detail information concerning recent clinical trials using cytokines, chemokines and chemokine antagonists for stem cell mobilization, and present novel strategies under development to make stem cell collections more effective. Because of the rarity of HSC, many of the studies exploring mechanisms of HSC mobilization have instead measured hematopoietic progenitors (HPC). HPC include both HSC and more committed hematopoietic progenitors, such as colony-forming cells (CFU-C). The correlation between HSC and HPC mobilization appears to be quite strong, nonetheless, this point merits consideration.

MECHANISMS OF HSC MOBILIZATION

Bone Marrow Microenvironment

Hematopoietic cells in the bone marrow (BM) exist in a highly organized three-dimensional microenvironment comprised of a diverse population of stromal cells and an extracellular matrix (ECM) rich in fibronectin, collagens, and various proteoglycans. HSC are spatially distributed into specific BM microenvironment niches. There is evidence that osteoblasts play a key role in regulating HSC function, and a fraction of HSC are physically associated with osteoblasts at the endosteum of the BM, defining the endosteal stem cell niche [Petit et al., [2002]]. Kiel et al. [2005] showed that a significant fraction of HSC in the BM were closely association with sinusoidal endothelial cells, suggesting that "endothelial niches" for HSC also exist. It is likely that HSC interaction with the different types of stromal cells in the endosteal and endothelial niches plays an important role in regulating HSC trafficking as well as self-renewal, proliferation, and differentiation.

To enter the circulation, HSC must migrate through the vascular barrier (termed the BM-blood barrier) that separates the hematopoietic compartment from the circulation. BM venous sinuses are the sites of leukocyte egress from the hematopoietic compartment and represent the only complete barrier to the intravascular space. The sinus wall is a trilaminar structure composed of endothelial cells, a basement membrane, and a layer of adventitial cells. Electron microscopy studies have demonstrated that there are numerous sites within the endothelial cell where luminal and abluminal membranes are fused, forming structures referred to as *diaphragmed fenestra*. Although not proven for HSC, it is through these fenestrations that mature hematopoietic cell egress occurs.

Adhesion Molecules Regulating HSC Trafficking

VLA4

Very late antigen-4 (VLA-4 or $\alpha_4\alpha_1$ integrin) is expressed on the majority of HPC in a low-affinity state; however, in response to cytokines such as GM-CSF, interleukin-3, and stem cell factor its function can be rapidly and transiently activated to promote adhesion to fibronectin. Although VLA-4 can bind to several ligands present in the BM environment, its interaction with vascular cell adhesion molecule-1 (VCAM-1) has been identified as a key pairing (Fig. 1). VCAM-1 is constitutively expressed by endothelial cells and stromal cells in the BM. The importance of VCAM-1/VLA-4 interactions to HSC trafficking in the BM has been confirmed by studies showing that antibodies directed against VCAM-1 or VLA-4 lead to HPC mobilization [Papayannopoulou and Nakamoto, [1993]; Papayannopoulou et al., [1995]]. Moreover, a report showed that the inducible deletion of $\alpha 4$ integrins in adult mice results in constitutive HSC mobilization [Scott et al., [2003]]. Interestingly, anti-VLA-4 induced HSC mobilization is significantly enhanced in CD18 ($\beta 2$-integrin) deficient mice or in wild-type mice treated with anti-$\beta 2$-integrin antibodies, suggesting that both VLA-4 and $\beta 2$-integrins contribute to the anchoring of HSC in the BM [Papayannopoulou et al., [2001]] (Fig. 2).

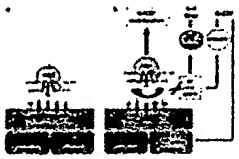

Figure 1. G-CSF HSC mobilization. a: There are adhesive interactions between HSC and matrix components in the BM. HSC express a wide range of cell adhesion molecules (CAM) including CXCR4, VLA-4, c-kit, CD62L, and CD44. The BM stroma expresses cognate ligands for these CAMs such as SDF-1, VCAM-1, KL, PSGL, and HA. b: HSC mobilization results from cytokine-induced functional changes in the adhesion profile expressed by the HSC in their relation to the BM stromal cells, osteoblasts, and other matrix components. G-CSF induces, through an

unknown cell, the release of a number of proteases into the BM, including NE, CG, and MMP9. IL-8 and Groâ release the same enzymes via neutrophils and monocytes. These proteases cleave several adhesion molecules thought to play an important role in HSC trafficking and mobilization, including c-kit, VCAM-1, CXCR4, and SDF-1. Recent data suggest that G-CSF treatment potently inhibits osteoblast SDF-1 expression at the mRNA level furthermore osteoblasts are the major source of SDF-1 in the BM. The resultant decrease in osteoblast SDF-1 may also contribute to enhanced HSC mobilization especially in response to G-CSF. Cathepsin G (CG), chemokine receptor-4 (CXCR4), hematopoieic stem cell (HSC), hyaluronic acid (HA), interleukin 8 (IL-8), kit ligand (KL), matrix metalloproteinase-9 (MMP-9), neutrophil elastase (NE), stromal cellderived factor-1 (SDF-1), vascular cell adhesion molecule-1 (VCAM-1), very late antigen-4 (VLA-4), P-selectin glycoprotein ligand-1 (PSGL). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
[Normal View 49K | Magnified View 101K]

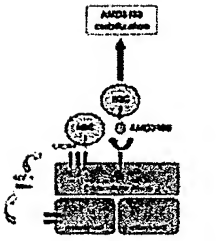

Figure 2. AMD3100 HSC mobilization. CXCR4/SDF-1 axis plays a critical role in HSC homing and mobilization. Disruption of the CXCR4/SDF-1 interaction with the CXCR4 competitive inhibitor AMD3100 results in rapid mobilization of HSC into the peripheral blood. Chemokine receptor-4 (CXCR4), hematopoieic stem cell (HSC), stromal cell-derived factor-1 (SDF-1). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
[Normal View 33K | Magnified View 61K]

CD44

The glycosaminoglycan hyaluronan (HA) has been shown to participate in the adhesion of HSC to ECM and stromal cells. Two major receptors for HA on HSC have been identified, CD44 and RHAMM. Expression of CD44 and RHAMM is reduced in mobilized HPC versus steady-state BM HPC, suggesting a possible role for HA receptors in mobilization [Pilarski et al., [1999]]. Consistent with this premise, mice lacking CD44 have an impaired mobilization response to G-CSF [Schmits et al., [1997]], and treatment of mice with an anti-CD44 antibody results in a modest mobilization of HPC to the blood [Vermeulen et al., [1998]]. Finally, inhibition of CD44 signaling in human HPC inhibited their homing to the BM in NOD/SCID mice [Avigdor et al., [2004]]. Collectively, these studies suggest that CD44 is a key adhesion molecule regulating HSC trafficking in the BM.

Selectins

The selectin family of adhesion molecules contains three family members. P- and E-selectin are expressed on endothelial cells, and their expression is induced in response to inflammatory signals, while L-selectin is constitutively expressed on mature leukocytes and HPC. Endothelium selectin-deficient mice exhibit marked leukocytosis, splenomegaly, and increased levels of circulating HPC, suggesting that selectins may play a role in regulating HPC trafficking [Bullard et al., [1996]; Frenette et al., [1996]]. Indeed, homing of HPC to the BM of P- and E-selectin deficient mice is defective [Frenette et al., [1998]]. To explore their role in HPC mobilization, two independent groups treated mice with fucoidan, a sulfated glycan that inhibits selectin function in vivo [Frenette and Weiss, [2000]; Sweeney et al., [2000]]. Both studies showed that fucoidan induced significant mobilization of HPC to the blood, even in mice lacking L-, P- and E-selectin, suggesting that the mode of action of fucoidan is not via blockade of the known selectins.

uPAR

Urokinase-type plasminogen activation receptor (uPAR) binds and activates urokinase and modulates cell adhesion and migration through regulation of integrin activation. uPAR is a GPI-anchored protein that can be shed from the cell surface. Soluble uPAR inhibits CD34 migration [Selleri et al., [2005]]. Interestingly, serum levels of soluble uPAR levels increase during G-CSF induced mobilization [Selleri et al., [2005]]. A preliminary study reported that G-CSF mobilization is impaired in uPAR-deficient mice, providing further evidence that this receptor may be an important regulator of HSC adhesion and migration in the BM [Tjwa et al., [2005]].

General Features of HSC Mobilization

Diversity of mobilizing agents

One striking feature of HSC mobilization is the diversity of mobilizing agents. A large number of hematopoietic growth factors, certain chemokines, and cytotoxic chemotherapeutic agents, can induce HSC mobilization. Interestingly, hematopoietic growth factors with distinct target cell populations and biological activities share the ability to mobilize HSC. For example, hematopoietic growth factors that predominantly affect myeloid cells (G-CSF and granulocyte-macrophage

colony-stimulating factor), T- and B-lymphocytes (interleukin-7), and natural killer cells (interleukin-12) are all potent mobilizing stimuli.

Kinetics of HSC mobilization

Most hematopoietic growth factors induce HSC mobilization with delayed kinetics. For example, with G-CSF, peak levels of circulating HSC are achieved after 4-5 days of treatment. In contrast, mobilization with chemokines typically peaks within hours of administration.

Phenotype of mobilized HSC

Hematopoietic growth factor-mobilized HPC have characteristic phenotypic features that are distinct from HPC that reside in the BM under steady-state conditions. Most notably, relative to BM HPC, a higher percentage of mobilized blood HPC are in the G_0 or G_1 phase of the cell cycle. A study showed that HPC are selectively mobilized after the M phase of the cell cycle, providing a potential explanation for preponderance of HPC in the G_0 or G_1 phase of the cell cycle in the blood [Wright et al., [2002]]. Compared with BM resident HPC, circulating HPC display reduced expression of VLA-4 [Mohle et al., [1993]; Watanabe et al., [1997]] and c-kit [Mohle et al., [1993]] on their cell surface.

Role of Proteases

Neutrophil serine proteases

A highly proteolytic microenvironment is induced in the BM during HPC mobilization by G-CSF [Levesque et al., [2002]]. The neutrophil serine proteases, neutrophil elastase (NE) and cathepsin G (CG) accumulate in the BM with kinetics that mirror that for HSC mobilization [Levesque et al., [2002]]. Moreover, expression of serpina1 and serpina2, naturally occurring inhibitors of these proteases, is markedly reduced after G-CSF treatment [Winkler et al., [2005]]. NE and CG are capable of proteolytic cleavage of key molecules regulating HSC trafficking in the BM, namely VCAM-1 [Levesque et al., [2001]] and SDF-1 [Petit et al., [2002]]. However, mice lacking NE and CG display normal G-CSF induced HSC mobilization [Levesque et al., [2004]], consequently the role of NE and CG in HSC mobilization remains unclear.

Metalloproteinases

Matrix metalloproteinase-9 (MMP-9 or gelatinase B) accumulates in the plasma and/or BM following mobilization with interleukin-8, G-CSF, or cyclophosphamide [Pruijt et al., [1999]; Levesque et al., [2002]]. A direct role for MMP-9 in HSC mobilization has been postulated. Neutralizing antibodies to MMP-9 attenuate IL-8 induced mobilization in rhesus monkeys [Pruijt et al., [1999]]. However, we and others [Pruijt et al., [2002]; Semerad et al., [2005]], showed that IL-8 induced HSC mobilization is normal in MMP-9 deficient mice, raising the possibility that there may be species-specific differences in the requirement for MMP-9 to mediate IL-8 induced HPC mobilization.

MMP-9 also has been implicated in G-CSF-induced HPC mobilization in mice. Heissig et al. [2002] reported that HSC mobilization by G-CSF was significantly impaired in MMP-9 deficient mice or wild-type mice treated with a broad-spectrum metalloproteinase inhibitor. The authors showed that MMP-9 cleaved Kit-ligand from the surface of BM stromal cells, providing a potential mechanism. In contrast, we and others have shown that G-CSF induced HSC mobilization in MMP-9 deficient mice is normal [Papayannopoulou et al., [2003]]. Though the reason for the discrepancy between these studies is unknown, it is possible that the different genetic strains of mice used may account for the observed differences. In any case, these data definitively show that HSC mobilization by G-CSF is not absolutely dependent upon MMP-9.

CD26

CD26 (dipeptidylpeptidase IV), a membrane-bound extracellular serine-protease expressed on a subset of HPC, inactivates CXCL12 through proteolytic cleavage [Christopherson et al., [2003a]]. G-CSF induced HPC mobilization is defective in CD26 deficient mice or in wild-type mice treated with a specific CD26 inhibitor [Christopherson et al., [2003a], [b]], and CD26-deficient HPC display enhanced homing to the BM and long-term engraftment potential [Christopherson et al., [2003a]].

SDF-1/CXCR4 Signaling

Role of SDF-1/CXCR4 in HSC trafficking

There is convincing evidence that interaction of stromal cell derived factor-1 (SDF-1/CXCL12) with its cognate receptor, CXCR4, generates signals that regulate HSC trafficking in the BM. SDF-1 is a CXC chemokine constitutively produced in the BM by stromal cells [Pelus et al., [2002]]. It is a potent chemoattractant for HSC and has been shown to regulate cell adhesion, survival, and cell-cycle status. Studies of SDF-1 or CXCR4 deficient mice have established that these genes are necessary for the normal migration of HSC from the fetal liver to the BM and in the efficient retention of myeloid precursors in the adult BM [Kawabata et al., [1999]; Ma et al., [1999]]. Elevation of SDF-1 levels in the blood by administration of CXCL12 or by injection of an adenoviral vector expressing CXCL12 is associated with a significant mobilization of HSC into the blood. Finally, as discussed in more detail below, treatment with AMD-3100, a specific antagonist of CXCR4, induces rapid and robust HSC mobilization in both humans and mice [Liles et al., [2003]; Broxmeyer et al., [2005]].

Regulation of SDF-1 expression in the bone marrow

There is accumulating evidence that disruption of SDF-1/CXCR4 signaling is a key step in HSC mobilization by G-CSF. SDF-1 protein levels in the BM fall sharply during G-CSF-induced mobilization [Petit et al., [2002]; Semerad et al., [2002]; Levesque et al., [2003]]. The magnitude of the decrease in SDF-1 protein expression correlates well with the magnitude of HSC mobilization [Semerad et al., [2005]]. There also is evidence that CXCR4 on HSC may be proteolytically inactivated during G-CSF treatment [Levesque et al., [2003]], further disrupting SDF-1/CXCR4 signaling.

The mechanisms that regulate SDF-1 expression in the BM are controversial. Previous reports suggested that NE and CG might regulate SDF-1 protein expression in the BM through proteolytic cleavage of SDF-1 [Petit et al., [2002]; Levesque et al., [2003]]. However, mice genetically lacking NE and CG display normal G-CSF induced HPC mobilization, and the expected decrease in BM SDF-1 protein was observed [Levesque et al., [2004]]. Thus, the G-CSF-induced decrease in SDF-1 protein expression in the BM does not require these proteases. Recently, we showed that SDF-1 mRNA expression decreases sharply during G-CSF induced HSC mobilization and in fact, correlates well with SDF-1 protein expression [Semerad et al., [2005]]. These data suggest that G-CSF regulates SDF-1 expression in the BM primarily at the mRNA level. A potential mechanism for this is suggested by the observation that G-CSF treatment potently suppresses osteoblasts, the major source of SDF-1 in the BM [Semerad et al., [2005]].

DIFFERENCES BETWEEN BONE MARROW-HPC AND PERIPHERAL BLOOD-HPC

Transplantation of mobilized autologous PBSC has replaced BM transplantation as the preferred method for hematopoietic recovery after myeloablative chemotherapy or chemoradiotherapy, and is widely used for allo-SCT. In addition to reducing donor morbidity, the use of mobilized PBMC has resulted in higher $CD34^+$ content of grafts, shorter hospital stay, and reduced engraftment times for both neutrophils and platelets, as well as improved lymphocyte recovery with an enhanced immunologic reconstitution when compared to patients receiving BM [Korbling et al., [1995]; Bensinger et al., [1996]]. The dose of $CD34^+$ cells infused per kilogram of patient body weight influence marrow recovery both qualitatively and quantitatively, in the auto or allo-SCT setting [Bensinger et al., [1995]; Weaver et al., [1995]]. In auto-SCT, the infusion of 2.5×10^6 $CD34^+$ cells/kg results in adequate hematopoietic engraftment [Bensinger et al., [1995]], but increasing the dose to 5×10^6 $CD34^+$ cells/kg is consistently associated with more predictable and rapid recovery, especially platelet recovery [Shpall et al., [1997]]. Furthermore, recent data suggest that there is a continuous dose-response relationship between the number of $CD34^+$ cells infused and hematopoietic recovery. The neutrophil engraftment (ANC > 500/μl) after the re-infusion of PBSCs that had been mobilized with hematopoietic growth factors occurs at a median of 9-14 days, and platelet engraftment (>20,000/μl) occurs at a median of 10-17 days [Bensinger et al., [1995]; Schmitz et al., [1996]].

Based on the benefits described for auto-SCT, cytokine-mobilized PBSC were explored as source of cells for allo-SCT. Initial concern focused on the risk of normal donors developing secondarily acute leukemias. Long term follow-up studies of normal donors have thus far failed to demonstrate any increased risk for this normal donor population [Cavallaro et al., [2000]]. Another concern was the possibility for increased risk of GvHD in light of 10- to 50-fold increased numbers of T cells present in the mobilized PBSC products. A large number of small phase II studies were performed using mobilized PBSCs as a source of HSC for allo-SCT. Rates of acute GvHD were similar to those when BM was used as source of allo HSC. Some of these studies showed an increased risk for limited and extensive chronic GvHD [Storek et al., [1997]; Brown et al., [1999]]. Similar to auto-SCT studies, the number of allogeneic $CD34^+$ cells infused correlated well with both neutrophil and platelet engraftment. The infusion of $>5 \times 10^6$ $CD34^+$ cells/kg had a 95% chance of both neutrophil and platelet engraftment by day +15, and no correlation could be found between GvHD or survival and the $CD3^+$ cells infused [Brown et al., [1997]]. In one retrospective study, infusion of $>8 \times 10^6$ $CD34^+$ kg was associated with decreased survival presumably due to increased rates of chronic GvHD [Przepiorka et al., [1999]].

The optimal method for mobilization of stem cells from the BM into the peripheral blood remains unknown.

DIFFERENT APPROACHES TO STEM CELL MOBILIZATION

HPC mobilization has been induced clinically in humans or experimentally in mouse using variety of approaches including: chemotherapeutic agents as cyclophosphamide or paclitaxel; cytokines such us G-CSF, GM-CSF, IL-7, IL-3, IL-12, stem-cell factor (SCF), and Flt-3 ligand; and chemokines as SDF-1, IL-8, or Groβ.

We will discuss different strategies used currently in clinic, and the most promising investigational agents currently in development.

Chemotherapy

Chemotherapy was the first mechanism discovered to mobilize HPC from the BM into periphery. Initially, the mobilization protocols were based in chemotherapy alone; however, since the discovery of human G-CSF cytokine mobilization has been the standard mobilizing agent alone or in combination with chemotherapy [Welte et al., [1985]].

Before the availability of hematopoietic cytokines, it was noted that marrow hypoplasia-producing chemotherapy such as those used for acute leukemia results in a transient increase in the number of HSC in the peripheral blood. The collection and further administration of these PBMC enriched in HSCs demonstrated rapid engraftment and clinical studies documented for first time the full hematopoietic reconstitution with autologous mobilized peripheral blood in the 1980s [Kessinger et al., [1986]; Reiffers et al., [1986]; Juttner et al., [1988]]. However, some patients, specifically patients with progressive disease, marrow infiltration, or prior exposure to alkylating agents or radiation therapy, failed to exhibit this response to chemotherapy and had insufficient collection for transplantation [To et al., [1990]]. Subsequently it was discovered that the administration of G-CSF or GM-CSF during the recovery from chemotherapy increased the number of HPC to levels as much as 1,000-fold higher than what was in the blood before treatment [Socinski et al., [1988]; Gianni et al., [1989]]. This initiated the exploration of efficacious mobilization regimens using hematopoietic cytokines, cytokine combinations, chemotherapy plus cytokines, and chemokines alone or in combination with cytokines.

Cytokines

Cytokines are small secreted proteins which mediate and regulate immunity, inflammation, and hematopoiesis. They are produced in response to an immune stimulus. They act by binding to specific membrane receptors, which then signal via second messengers, often tyrosine kinases, to modify the cell gene expression and cellular function such as proliferation, activation, and secretion of effectors molecules.

G-CSF is the most potent cytokine currently available for the mobilization of HPC. Administration of G-CSF at doses at least 10 μg/kg/day for 5 days is usually required to achieve the mobilization goal of 5×10^6 $CD34^+$ cells/kg of recipient body weight, a dose considered suitable for reproducible, rapid and consistent engraftment of both neutrophils and platelets [Henon et al., [1992]; Schmitz et al., [1996]]. In a randomized study of healthy volunteers that received 5 days of G-CSF (10 μg/kg/day), GM-CSF (10 μg/kg/day), or the combination of both, Lane et al. reported in the fifth day of treatment an average of 0.99 and 0.25% $CD34^+$ cells in the peripheral blood for G-CSF and GM-CSF, respectively. Each group underwent one leukapheresis collecting 119×10^6 and 12.6×10^6 $CD34^+$ for the G-CSF or GM-CSF treated donors respectively [Lane et al., [1995]]. The use of G-CSF to enhance the mobilization of $CD34^+$ cells and collection of stem cells using leukapheresis has become the standard of care for auto- and allo-SCT. CIBMTR and EBMT data show that over 90% of all auto-SCT in the world are performed using cytokine or chemotherapy/cytokine mobilized HSC [Anderlini et al., [2001]].

The toxicity of G-CSF has been defined in studies of allogeneic donors [Anderlini et al., [1996]; Akizuki et al., [2000]]. Approximately 85% of donors develop somatic complaints, of which skeletal pain is most prominent. The pain begins after a single filgrastim injection and plateaus after two to three injections. Other side effects include fatigue, headache, and rarely nausea. These complaints are generally tolerable, and few donors require a dose reduction or discontinuation of the drug. G-CSF mobilization also causes some alterations in serum chemistries as LDH, AP and ALT increase 2- to 4-fold after five daily doses. The serum levels of potassium, BUN and magnesium may show minimal declines during the treatment. Few serious complications have been reported. Spontaneous splenic rupture occurred in two normal donors; in both cases the spleen was surgically removed and disclosed extensive extramedullary hematopoiesis. Filgrastim may precipitate severe sickle crisis in persons with sickle cell anemia, and there is one fatal case reported [Adler et al., [2001]]. Growth factors should not be given to donors with history of autoimmune disorders, because flares of the disease have been reported after filgrastim administration [de Vries et al., [1991]]. There is one fatal myocardial infarction and one fatal cerebral vascular accident reported few days after cytokine mobilization, although any relationship of these events to the donation process remains unclear. Some reports have showed that G-CSF administration induces a transient and reversible hypercoagulable state, and therefore, caution must be applied when considering donors with history of a coagulation disorder, peripheral vascular disease, myocardial infarction, or stroke [Gutierrez-Delgado and Bensinger, [2001]]. The long-term safety profile of growth-factor therapy in normal individuals has not been established. There have been several reports providing 1-5 years follow-up on limited number of PBSC donors [Stroncek et al., [1997]; Anderlini et al., [2002]]. In no instance have serious adverse events, including acute leukemia, attributable to filgrastim been identified.

Chemotherapy + Cytokines

The use of chemotherapy in combination with cytokines (both G-CSF and GM-CSF) has been used to both enhance HSC mobilization and to reduce contamination with malignant cells. The sequential use of cytotoxic chemotherapy followed by the administration of G-CSF or GM-CSF has consistently resulted in enhanced $CD34^+$ cells collected, but is associated with an increased risk of neutropenia, infections and costly hospitalizations [Ravagnani et al., [1990]; Bensinger et al., [1995]]. No randomized trials have clearly compared and contrasted the role of cytokine alone versus cytokine following chemotherapy for stem cell mobilization. Furthermore no studies have demonstrated significant benefits of this approach such as shorter transplant hospitalizations, reduced disease free survival or overall survival with any malignancy following transplantation [Weaver et al., [1995]; Narayanasami et al., [2001]].

Investigational Agents

AMD-3100

Several chemokines, small chemoattractant molecules that regulate leukocyte migration and trafficking, have emerged as key agents for HPC mobilization. Some examples are SDF-1, IL-8, monocyte chemoatractant protein-1, macrophage

inflammatory protein 1a or 1b, and Groβ. A hallmark of chemokine mobilization is its rapid mobilization kinetics with peak CD34/ml occurring in minutes to hours after administration versus 4-6 days required for G-CSF and GM-CSF.

AMD3100 is the most promising mobilizing agent currently in clinical development. AMD3100 is a bicyclam molecule that specifically and reversibly blocks SDF-1 binding to CXCR4. It was initially developed as an antagonist of the CXCR4 HIV coreceptor on CD4+ T cells thus blocking HIV entry. In the first phase I study AMD3100 was well tolerated by 12 healthy volunteers at doses up to 80 μg/kg intravenous (iv) or subcutaneous (s.c.). All adverse events were mild and reversible. Interestingly, all patients experienced a transient leukocytosis [Hendrix et al., [2000]].

In another phase I study with 26 healthy volunteers, a single subcutaneous injection of AMD3100 was administered which resulted a reversible dose-dependent increase in the $CD34^+$ cells mobilized into the peripheral blood [Liles et al., [2003]]. This event was evident within 1 h and the peak effect was observed after 240 μg/kg dose s.c., with a 15-fold increase in $CD34^+$ cells 9 h after a single injection and declined to baseline by 24 h.

An additional phase I study assessed the safety and clinical effects of AMD3100 in patients with multiple myeloma (MM; n = 7) and non-Hodgkin's lymphoma (NHL; n = 6). Patients received a single dose of AMD3100 (160 or 240 μg/kg s.c.), causing a rapid and significant increase in the total WBC and PB $CD34^+$ counts at both 4 and 6 h. $CD34^+$ cell count increased 5.1- and 6.2-fold from the baseline at 4 and 6 h respectively. The absolute $CD34^+$ cell counts observed at 4 and 6 h were higher in the 240 μg/kg group compared with the 160 μg/kg group (72 and 83% higher respectively) [Devine et al., [2004]].

AMD3100 pharmacokinetic studies indicate that the drug is rapidly absorbed after s.c. injection and eliminated from plasma in a biexponential manner [Lack et al., [2005]]. Broxmeyer et al. showed that AMD3100 induced rapid mobilization of mouse and human HPC and synergistically increased G-CSF induced mobilization of HPC. They also showed that AMD3100 mobilized murine PBSC could be used to provide long-term multilineage engraftment of primary and secondary transplant recipients. Furthermore, human $CD34^+$ mobilized from normal volunteers in response to a single dose of AMD3100 efficiently engrafted non-obese diabetic-severe combined immunodeficiency (NOD-SCID) mice. AMD3100 mobilized human CD34 were as effective or more effective than G-CSF mobilized human CD34 for engraftment of NOD-SCID mice [Broxmeyer et al., [2005]].

AMD3100 was administered (160 μg/kg s.c. on day 5) after 5 days of G-CSF (10 μg/kg s.c.) to normal volunteers [Liles et al., [2005]]. The combination of G-CSF + AMD3100 resulted in 3.8-fold increase of $CD34^+$ cells/kg harvested after a routine leukapheresis procedure. In addition to demonstrating the synergistic effect of AMD3100 plus G-CSF, this group also demonstrated that a single dose of 240 μg/kg of AMD3100 could yield similar $CD34^+$ cells/kg after a single leukapheresis when compared to the same normal volunteers mobilized with G-CSF (10 μg/kg/day) for 5 days.

Recently, Flomenberg et al. [2005] showed that the use of AMD3100 plus G-CSF for autologous HPC mobilization in patients with MM (n = 10) or NHL (n = 15) is superior to the standard G-CSF alone. Patients were randomly assigned to an initial mobilization with G-CSF versus G-CSF + AMD3100 (160 or 240 μg/kg on day 4, 10 h previous the first pheresis. After collection of $\geq 2 \times 10^6$ CD34/kg and a rest period of 1 week, each patient was mobilized with the alternative regimen allowing each person to serve as their own control. The combination of G-CSF + AMD3100 was a superior mobilizing regimen compared to G-CSF regardless of which regimen the patient was first mobilized with. In 21/25 (84%) patients the combination of G-CSF + AMD3100 resulted in a daily increase in the number of $CD34^+$ cells collected by over 50% compared to G-CSF. In nine patients, it was not possible to collect the minimum of 2×10^6 $CD34^+$ cells/kg with G-CSF alone. In each case in which patients failed to mobilize $>2 \times 10^6$ $CD34^+$ cells/kg in response to G-CSF alone, the combination of G-CSF + AMD3100 was successful. The combination of G-CSF + AMD3100 resulted in the mobilization of >5 × 106 $CD34^+$ cells/kg after ≤4 apheresis procedures in 80% of patients compared to only 32% of those patients mobilized with G-CSF alone.

The use of AMD3100 alone to mobilize autologous PBSC is being explored in "good mobilizer" myeloma patients. In addition AMD3100 alone is being tested to mobilize stem cells from normal HLA matched sibling donors in preparation for allo SCT[103]. Currently five patients have been transplanted after collection of $>2 \times 10^6$ $CD34^+$ cells/kg allogeneic stem cells after a single injection of AMD3100. All patients engrafted neutrophils and platelets and long-term studies are underway to accrue more patients and to examined other endpoints such as GvHD, relapse free survival, long term stable engraftment and overall survival [Devine et al., [2004]]. This allogeneic transplant study was based on the preclinical results in the mouse demonstrating consistent short-term and long-term engraftment after the administration of AMD3100 mobilized HPC and similar rates of acute GvHD in animals receiving AMD3100 mobilized T cells and G-CSF mobilized T cells [Broxmeyer et al., [2005]].

CXCR4 peptide

CTCE-0021 is a novel cyclized CXCR4 agonist peptide (SDF-1α analog) developed to stabilize the SDF-1 α-helix to

increase their bioactivity, and terminating the C-terminus as an amide to reduce its immunogenicity. This compound retains comparable CXCR4 receptor agonist activity. In mice, a single bolus administration of CTCE-0021 demonstrated a rapid dose-dependent mobilization of HPC between 5 min and 4 h post-dosing, with an increase in WBC resulted from an increase in granulocytes within 5 min post-dosing that persisted for approximately 24 h. The mechanisms involved in this CXCR4 agonist peptide mobilization remains unknown, but Pelus et al. suggested that CTCE-0021 mobilization is associated with down-regulation of CXCR4 on HSC, and alteration in the plasma to marrow SDF-1 gradient [Fukuda et al., [2005]]. CTCE-0021 is an efficient and rapid mobilizer of PMN and HPC when used alone and shows synergistic activity when used in combination with G-CSF.

Stem-cell factor (SCF)

Recombinant human SCF (rHuSCF) is a cytokine that stimulates pre-lineage-committed HPC. Most clinical studies of (SCF) report the use of this agent with other cytokines. Limited reports of SCF by itself are available and this cytokine appears to result in a dose-dependent six- to tenfold mobilization of CFU-GM [Morstyn et al., [1994]]. One phase II study demonstrated enhanced mobilization when SCF was used in conjunction with G-CSF to mobilize stem cells from lymphoma patient undergoing auto-SCT [Moskowitz et al., [1997]]. Recently, rHuSCF (20 μg/kg/day) when combined with G-CSF (10 μg/kg/day) was shown to enhance mobilization of HPC in heavily pretreated patients who have failed a previous attempt with G-CSF alone [Dawson et al., [2005]]. In this study, 29/48 (60%) achieved a cumulative total of $>2.0 \times 10^6$ $CD34^+$ cells/kg following remobilization with SCF and G-CSF after initial failure with G-CSF alone. Due to occasional anaphylactoid reactions to SCF, including angioedema, urticaria, pruritus, and laryngospasm [Costa et al., [1996]], the FDA decided not to approve the agent for use as an agent to enhance autologous stem cell mobilization in the United States. SCF is approved for use in Canada and New Zealand.

Gro-β

Gro-β is a member of the CXC chemokine family, which includes the related ligands Gro-, Gro-, ENA78, NAP-2, GCP-2, IP10, and interleukin-8 (IL-8), and it has biological activities related to specific binding to the CXCR2 receptor. SB-251353 is a recombinant N-terminal 4-amino acid truncated form of the human chemokine GRO specifically binds only to CXCR2 and with greater potency than full-length **Gro-β**. The human CXCR2 selective ligand SB-251353 induces rapid mobilization of hematopoietic stem and progenitor cells in mice and monkeys and synergizes with G-CSF [Hepburn et al., [2001]; King et al., [2001]]. Initially, chemokine administration is associated with a leukopenia within 5 min of injection followed by a period of neutrophilia 30-45 min later. The combination of SB-251353 with G-CSF resulted in augmented stem cell mobilization compared with the use of G-CSF alone. The mechanism of action of SB-251353-induced stem and progenitor cell mobilization appears similar to IL-8, which involves up-regulation of MMP-9 activity.

IL-8

IL-8 is a CXC chemokine produced by a variety of cells including monocytes, neutrophils, fibroblasts, and endothelial cells, induced by proflammatory cytokines as TNFα, IL-1, IL-2, IL-3, and GM-CSF. IL-8 induces a rapid mobilization of HSC in 30-60 min [Laterveer et al., [1995]]. This mobilization is prevented by pretreatment with an inhibitory anti-gelatinase B antibody, indicating that MMP-9 is involved as a mediator of IL-8-induced mobilization of HSC. Neutrophils are indispensable for IL-8-induced HSC mobilization. This process is abolished in mice that are rendered neutropenic after administration of a depleting anti-GR-1 Ab, and is restored upon the infusion of purified neutrophils [Pruijt et al., [2002]]. Also, neutralizing Abs against the β_2 integrins lymphocyte function-associated molecule 1 (LFA-1) and Mac-1 (CD11b) prevented IL-8-induced HSC/HPC mobilization [Pruijt et al., [1998]].

Recombinant human growth hormone (rhGH)

Growth hormone is a pleiotropic cytokine targeting a variety of nonhematopoietic and hematopoietic cells by binding to its specific receptor [Kopchick and Andry, [2000]]. In vitro, rhGH increases colony formation by HPC (CFU-GM and BFU-E) [Merchav et al., [1988]]. In vivo, a 7-day course of rhGH in mice significantly induces HPC mobilization into peripheral blood [Carlo-Stella et al., [2004b]]. Carlo-Stella et al. investigated rhGH administration associated with chemotherapy plus G-CSF (5 μg/kg/day × 5 days) for enhancing stem cell mobilization in 16 patients with relapsed or refractory hematological malignancies who had failed a first mobilization attempt with chemotherapy plus G-CSF [Carlo-Stella et al., [2004a]]. Patients were then re-mobilized with chemotherapy, G-CSF (5 μg/kg/day × 5 days) and rhGH (100 μg/kg/day, maximum daily dose of 6 mg). This combination resulted in efficient mobilization and collection of $\geq 5 \times 10^6$ $CD34^+$ cells/kg in 87% of these poor mobilizers with a median of 3 leukapheresis (i.e., from 1.1×10^6/kg up to 6×10^6/kg). The exact mechanism by which rhGH restores stem cell mobilization capacity in heavily pretreated patients with relapsed or refractory hematological malignancies is not clear, but is probably related to the expansion of HSC or HPC which become susceptible to be released upon a subsequent or concomitant stimulus, such as G-CSF.

hrPTH

Calvi et al. [2003] showed haematopoietic stem cells derive regulatory information from bone, accounting for the localization of haematopoiesis in BM. They showed that PTH/PTHrP receptors-stimulated osteoblastic cells that are increased in number produce high levels of the Notch ligand, Jagged-1, and support an increase in the number of haematopoietic stem cells with evidence of Notch1 activation in vivo. Furthermore, ligand-dependent activation of PTH/PTHrP receptors with parathyroid hormone (PTH) increased the number of osteoblasts in stromal cultures, and

augmented ex vivo primitive haematopoietic cell growth that was abrogated by gamma-secretase inhibition of Notch activation. An increase in the number of stem cells was observed in wild-type animals after PTH injection, and survival after BM transplantation was markedly improved. Therefore, they showed that osteoblastic cells are a regulatory component of the haematopoietic stem cell niche in vivo that influences stem cell function. Niche constituent cells or signaling pathways provide pharmacological targets with therapeutic potential for stem-cell-based therapies.

Pegfilgrastim

Pegylated G-CSF has a prolonged half life and was approved by the FDA in the USA to prevent prolonged neutropenia following chemotherapy for non-hematological malignancies. The administration of a single dose of 30-300 μg/kg pegfilgrastim resulted in a significant mobilization of $CD34^+$ cells in healthy donors [Molineux et al., [1999]]. Current trials are underway to determine the relative efficacy of pegylated G-CSF as a mobilizing agent for both patients undergoing autologous stem cell transplantation and for normal sibling donors who are donating stem cells for HLA-matched allo-SCT.

TPO

Thrombopoietin (TPO) is a cytokine that regulates megakaryocytopoiesis. Some studies have showed that it also induces mobilization of $CD34^+$ [Vadhan-Raj et al., [1997]], and it synergizes with G-CSF to enhance stem cell mobilization. Currently no thrombopoietins have been approved by the FDA.

FACTORS AFFECTING MOBILIZATION IN RESPONSE TO CITOKINES

The aim of PBSC mobilization is to obtain at least 2×10^6 $CD34^+$ cells/kg recipient body weight in order to obtain a rapid engraftment of neutrophils and platelets. There is a good correlation between the $CD34^+$ cell count in peripheral blood and the yield in the PBSC collection. Several reports suggest an inverse relationship with adhesion molecule expression on HSC and good mobilization. Consistent with this hypothesis, HSC from "good mobilizers" express lower CXCR4, and VLA-4 than those "poor mobilizers" [Gazitt and Liu, [2001]; Gazitt et al., [2001]]. One group suggest an inverse correlation with plasma SDF-1 levels and $CD34^+$ CXCR4 expression with good mobilization in response to G-CSF. SDF-1 gene polymorphism has been proposed as a conditional factor for $CD34^+$ cell mobilization [Benboubker et al., [2001]].

In auto-SCT, there are some factors that reduce mobilization, which include advanced age, prior radiotherapy, low platelet count, certain diseases as Hodgkin's disease, non Hodgkin's lymphoma, and myelodysplasia, and extensive prior cytotoxic chemotherapy, especially treatment with alkylating agents (melphalan, carmustine). The mobilization capacity of patients with hematological malignancies is in general lower than in patients with solid tumors such as breast or testicular cancer [Weaver et al., [1998]]. Some authors reported higher probabilities of mobilization failure in woman than in men [Perea et al., [2001]], but this could be related more to differences in ideal body weight between men and woman.

Patients that fail initial cytokine mobilization, or with high risk conditions, could be mobilized with increased doses of G-CSF (12.5-50 μg/kg/day × 5 days) [Kobbe et al., [1999]]. Other approaches include the use of concomitant chemotherapy and cytokines, G-CSF and GM-CSF, and in the near future G-CSF and AMD3100.

MOBILIZATION OF TUMOR CELLS

Active signaling through CXCR4/SDF-1 and other adhesion molecules are required for homing and mobilization of HPC. Gazzit and colleagues studied the surface expression of CXCR4, SDF-1 and VLA-4 on human myeloma cells mobilized with cyclophosphamide + GM-CSF and the SDF-1 plasma levels in the apheresis collection of patients undergoing mobilization for auto-SCT (n = 12). They observed a statistically significant decrease in the levels of serum SDF-1, and in the CXCR4 and VLA-4 expression on myeloma cells in the apheresis product compared to myeloma cells aspirated from BM prior to mobilization. These data suggest a role of CXCR4/SDF-1 in myeloma cell BM homing and mobilization [Gazitt and Akay, [2004]]. In a xenogeneic mouse model of human AML engraftment, the addition of neutralizing CXCR4 antibodies, SDF-1 antibodies, or AMD3100, blocked the tumor cell homing to the BM and spleen of NOD-SCID$\beta 2m^{null}$ mice [Tavor et al., [2004]] showing the importance of the CXCR4/SDF-1 axis in AML progression. Another elegant in vivo study using bioluminescence to track breast cancer cells in a mouse model, demonstrated substantial delay in the growth of lung metastasis when tumor cells were either treated with siRNA for CXCR4 or when animals were treated with AMD3100 [Smith et al., [2004]]. We developed a unique mouse model of human acute promyelocytic leukemia (APL). Our studies with this model suggest that CXCR4/SDF-1 are key regulators for leukemia migration and homing to the BM. After administration of AMD3100 (5 mg/kg sc) we observed a rapid and transient mobilization of leukemia cells from the BM into peripheral blood. G-CSF induced similar mobilization of mouse APL cells but with slower kinetics (4-5 days). Of note, AMD3100 mobilized mouse APL cells were found to be significantly more sensitive to genotoxic stresses of both daunorubicin and cytarabine in vivo. These results are consistent with many working with other leukemias and cancers, and suggest a protection effect of both adhesion and interaction with microenvironment [Garrido et al., [2001]; Hazlehurst et al., [2003]; Matsunaga et al., [2003]].

Although mobilization cell detachment of leukemia cells from the microenvironment may sensitize these cells to radiation and chemotherapy, the risk of contamination of mobilized PBSC products may be theoretically increased. Currently there remains no compelling data to support this and limited understanding of how the microenvironment exerts its protective effects.

CONCLUSION

A host of new drugs and new strategies have been developed to improve stem cell collection for patients undergoing autologous and allogeneic transplantation. These same mechanisms operative for HSC mobilization may apply to leukemia cell as well. Novel approaches of stem cell homing and mobilization discussed in this review may not only increase the number and quality of HSC mobilized but also provide insights into enhanced pharmacologic interventions resulting in improved HSC mobilization and enhanced egress of leukemic cells and thus sensitivity to anti-leukemia therapy.

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